IRIS Assessment Plan for Chloroform

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Outline of the Presentation

- Background
- Scoping Summary
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- Overall Objectives, Specific Aims, and PECO Framework

Background: Properties, Use and Exposure

- Chloroform, or $CHCl_3$, is a colorless, volatile liquid at room temperature with a distinctive odor.
- Formerly used as an inhaled anesthetic during surgery until about 1950, the primary use of chloroform today is in industry and research labs, where it is typically used as a solvent.
- Because of its volatility, chloroform tends to escape from contaminated media (e.g., water or soil) into air.
- Humans are most commonly exposed environmentally via inhalation of chloroform vapor from contaminated media (especially in indoor air) or through ingestion of chlorinated drinking water.
- Once inhaled or ingested, chloroform is rapidly absorbed and undergoes metabolism by cytochrome P450-dependent pathways. Metabolism occurs primarily in the liver, and to a lesser extent in the kidneys.

Background: Existing IRIS Assessment

- An IRIS assessment of chloroform currently exists and consists of: 1) an inhalation assessment, 2) an oral assessment, and 3) a mode of action (MOA) analysis for cancer.
- The inhalation assessment (posted in 1987) contains an inhalation unit risk (IUR) for chloroform based on liver tumors in rodents. This IUR was derived from an oral gavage study in mice employing a route-to-route extrapolation without the use of a PBPK model.
- No reference concentration (RfC) for chloroform currently exists on IRIS.
- The oral assessment (posted in 2001) contains a reference dose (RfD) for chloroform based on liver effects in dogs.
- A MOA analysis (also posted in 2001) concluded that chloroform is likely carcinogenic to humans by all routes of exposure, but only following high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues.
- Based on this MOA analysis, the RfD was determined to be protective with respect to cancer because, at the RfD, cytotoxicity—a key event in the MOA for cancer—was not observed.

Background: Existing IRIS Assessment (cont'd)

- The methodology used to derive the existing IUR has two shortcomings:
  1. It utilized a route-to-route extrapolation approach (i.e., oral to inhalation) that did not employ a PBPK model, and
  2. It incorporated a linear extrapolation approach for dose-response that implicitly assumed a risk of cancer at all nonzero exposures to chloroform (i.e., no threshold). This assumption is inconsistent with the MOA analysis.
- No RfC currently exists for chloroform on IRIS.
- These issues present difficulties when trying to evaluate risks associated with chloroform exposure via inhalation, and thus a need was identified to conduct a targeted update of the inhalation assessment for chloroform.

Scoping Summary

During scoping, the IRIS Program contacted EPA program and regional offices that had a potential interest in an updated IRIS assessment for chloroform to discuss their support for a targeted update of the inhalation assessment, as well as other specific assessment needs for this chemical.

Scoping Summary (cont'd)

EPA program and regional office interest in an updated chloroform assessment

Program or Regional Office	Inhalation	Statutes/Regulations	Anticipated Uses/Interest
OLEM	✓	Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) – Section 104	Up-to-date toxicity values (i.e., an RfC) are needed to set risk-based screening levels, derive baseline risks, establish clean-up levels, and evaluate clean-up progress at contaminated sites, many of which experience chloroform vapor intrusion.
Region 4	✓		Chloroform is present as a volatile contaminant at many industrial sites. Up-to-date toxicity values (i.e., an RfC) are needed to conduct regional risk assessment-related activities at these contaminated sites.
OAR	✓	Clean Air Act (CAA) – Section 112	Chloroform is classified as a hazardous air pollutant (HAP) under the Clean Air Act (CAA). OAR is mandated under CAA to periodically conduct risk and technology reviews (RTRs) for HAPs in which up-to-date toxicity values are needed to evaluate residual risk.

Scoping Summary (cont'd)

- The chloroform inhalation assessment will be updated by deriving an RfC based on available inhalation data from human or animal studies, and then this RfC will be evaluated in light of the existing MOA analysis for cancer.

- Derivation of an RfD and the analysis that determined the RfD was protective with respect to cancer will not be reevaluated as part of this update to the chloroform assessment because EPA program and regional offices did not express a specific need for an updated RfD for chloroform.

Initial Problem Formulation

- This targeted update will consider all adverse effects elicited by inhalation exposure to chloroform for which human or animal data are available.
- Based on a preliminary literature search:
  - The IRIS Program anticipates there will be less than 20 PECO-relevant studies identified for review.
  - The following health effects are likely to warrant inclusion in this assessment:
    1. nasal cavity effects,
    2. nervous system effects,
    3. liver and kidney effects,
    4. immune system effects, and
    5. reproductive/developmental effects.

Overall Objectives

- The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for these effects of chloroform to support development of toxicity values.
- The specific objective of this assessment is to derive an RfC for chloroform without the need for route-to-route extrapolation by using dose-response data from human or animal inhalation studies.
- In addition, the existing MOA analysis for cancer will be used to determine whether this newly derived RfC is protective with respect to cancer.

Specific Aims

- **Identify** literature reporting inhalation exposure to chloroform as outlined in the PECO framework and flag mechanistic studies for possible use in understanding potential human health hazards.
- **Conduct** study quality evaluations (risk of bias and sensitivity) for individual human and animal studies.
- **Extract** data on relevant health outcomes from human and animal studies based on the study quality evaluations.
- **Synthesize** the evidence across studies assessing similar health outcomes.
- **Evaluate** confidence in conclusions from across studies within human and animal evidence streams for each health outcome.
- **Integrate** results across evidence streams for each health outcome to conclude whether it is a hazard to humans (hazard identification).

Specific Aims (cont'd)

- **Derive** an RfC for chloroform, as supported by the available data (dose-response assessment).
- Subsequent to RfC derivation, evaluate the protectiveness of the RfC with respect to cancer based on the 2001 MOA analysis. [Note: *If the RfC is protective against cancer, the existing IUR would be removed from IRIS. If not, the available inhalation data will be evaluated to see if they are amenable to deriving a revised IUR for chloroform that would then replace the existing IUR.*]
- Identify issues concerning potentially susceptible populations and life stages.
- Characterize uncertainties through identification of key data gaps and research needs.

PECO Framework for Chloroform

PECO Element	Evidence
Populations	**Human**: All populations and life stages.
	Animal: Nonhuman mammalian animal species (whole organism) of any life stage.
	In vitro: Nonmammalian model systems; human or animal cells, tissues, or biochemical reactions with in vitro exposure regimens; bioinformatics pathways of disease analysis; or high throughput screening data.
Exposures	**Human**: Exposure to chloroform alone, including occupational exposures, via inhalation only.
	Animal: Exposure to chloroform alone via inhalation only.
	In vitro: Exposure to chloroform alone via growth or assay medium.
Comparators	**Human**: Any comparison or reference group exposed via inhalation to lower levels of chloroform, no chloroform, or chloroform for shorter periods of time.
	Animal: Lower or no exposure to chloroform via inhalation with concurrent vehicle control group.
	In vitro: Lower or no exposure to chloroform with concurrent vehicle control group.
Outcomes	All health outcomes (both cancer and noncancer) in humans and animals.